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Award Number: DAMD17-97-1-7030

TITLE: Magnetic Resonance Arterial Spin Tagging for Non-Invasive Pharmacokinetic Analysis of Breast Cancer

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REPORT DATE: October 2001

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	October 2001	Annual (30 Sep 00 - 29 Sep 01)

4. TITLE AND SUBTITLE
Magnetic Resonance Arterial Spin Tagging for Non-Invasive Pharmacokinetic Analysis of Breast Cancer

5. FUNDING NUMBERS
DAMD17-97-1-7030

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 Words)*

This research project concerns the development of MRI arterial spin tagging to non-invasively measure breast tissue perfusion. The specific aims are to (1) refine arterial spin tagging pulse sequences, (2) develop automated data analysis software, and (3) compare the technique to first-pass contrast-enhanced MRI and biopsy. The scope of effort has been mainly limited to technical developments. During the first two years, the spin-tagging pulse sequences were developed for the GE 1.5T Horizon LX CV/I MRI system at UC Davis. New image processing software, and software for statistical analysis of spin tagging and contrast enhanced dynamic scans, were written for use in the clinical setting. Year three and four (no cost extension) of the project included a clinical comparison with first-pass, contrast-enhanced MRI in 60 patients with unbiopsied breast masses, for aim (3). In the past year, these studies were not done, due to the inability to recruit patients, and no grant funds were spent. Official approval has been granted for a one-year no-cost extension. A new co-investigator, patient referral pattern, and support staff of the new Imaging Research Center at UC Davis should improve patient recruitment in this upcoming fifth year of the project.

14. SUBJECT TERMS
Breast Cancer

15. NUMBER OF PAGES
18

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

Table of Contents

Cover.....1

SF 298.....2

Introduction.....4

Body.....5

Key Research Accomplishments.....11

Reportable Outcomes.....12

Conclusions.....13

References.....14

Appendices.....15

Introduction

This research project concerns the development of MRI arterial spin tagging to non-invasively measure breast tissue perfusion. MR dynamic first-pass contrast-enhanced imaging has shown that malignant and benign breast lesions can be distinguished. However, it may have limited importance in clinical breast diagnosis due to significant false-negatives and false-positives. The arterial spin tagging technique was developed to measure tissue perfusion parameters without intravenous contrast, and has been successfully demonstrated in brain and kidney. The specific aims are to (1) refine arterial spin tagging pulse sequences and imaging protocols, (2) develop automated data analysis software for measurement of breast tissue parameters, and (3) compare the technique to first-pass contrast-enhanced MRI and biopsy. We will test the hypothesis that arterial spin tagging provides accurate and precise discrimination between normal tissue, benign and malignant lesions, when differences in perfusion and T_1 exist. Lesions will have been previously detected by clinically accepted diagnostic imaging procedures, and by biopsy. Statistical analysis will be performed to access the correspondence between arterial spin tagging and biopsy, and to establish the relative value of spin tagging compared to first-pass contrast-enhanced MRI. We hope to establish that, relative to using first-pass contrast-enhanced imaging, false positives and negatives are reduced using arterial spin tagging by virtue of increased image signal-to-noise ratio (SNR), higher spatial resolution, and the unique ability to obtain estimates of macromolecular bound fluid fractions. The scope of effort on the project is mainly limited to the technical aspects of development of a new methodology. However, the project also includes a performance comparison with the current gold-standard methodology. The technique will be evaluated in sixty patients, with roughly equal numbers of benign and malignant lesions.

Body

Summary of Project Accomplishments

Report for 2001

Between Sept 30, 2000 and Sept 29, 2001, the project has been inactive. No salary support was provided to the principal investigator or co-I, and there have been no direct cost expenses. As of Sept 2001, $ 69,719.04 (27% of total award) remain unexpended.

Report for 2000

David Zhu completed his dissertation (attached as Appendix) and compiled the software on CD-ROM (enclosed), a poster was presented at the BCRP meeting in Atlanta (attached as Appendix), and a publication is currently being written. Comparison of the arterial spin tagging sequence with the dynamic contrast enhanced first pass study, intended for year 3, has not yet been achieved. Sixty patients should have been studied at this point in the project, but only two have been studied. It was not possible to find a replacement physician for the original co-Investigator on the project, Rebecca Zulim, who left UCDMC November 1, 1998. I submitted a revised project schedule and budget in May 1999 based upon having Dr. Philip Schneider as a collaborator, and these were approved, but they were not implemented due to the lack of patient recruitment into the study. Although Dr. Schneider agreed to serve as a collaborator for this period, patient recruitment was ineffective. Over the past year, exactly $12,971 was spent from grant funds, for support of Dr. Zhu during the last three months (Oct 1999 - Dec 1999) of his employment at UC Davis, and 3% PI salary support. No salary support was provided to the co-I. As of Sept 2000, $71,408 (27.2% of total award) remain unexpended.

From the 1999 Annual Report ...

UCD Medical Center Radiology Department upgraded all their MRI systems from Signa Genesis 5.x to Signa LX 8.2.5, resulting in several months during which our pulse sequences were not compatible with any of the MRI systems to which we had access. Substantial time was needed to convert the pulse sequences to the LX 8.2.5 platform from the Genesis 5.x platform. This time period for upgrading the UCD Med Center MRI systems was not planned in advance, and the time to convert our research software was not written into the approved Work Statement. The graduate student on this project, David Zhu, and I succeeded in converting the arterial spin tagging pulse sequences, and on further developing new arterial spin tagging sequences based on our "odd-hybrid" EPI technique [Buonocore MH, Zhu DC. High spatial resolution EPI using an odd number of interleaves. Magnetic Resonance in Medicine 41 (6): 1199-1205 (1999)]. Also, advances have been made in our image processing software for the project. The major deficiency in our progress is with the third technical objective. Comparison of the arterial spin tagging sequence with the dynamic contrast enhanced first pass study has not yet been achieved. Rebecca Zulim, the co-I on the project, left UCDMC November 1, 1998, and a replacement was not immediately found. The budget and schedule was officially pushed back 6 months, into the 3rd year which had a light work schedule in the original proposal. The project now continues into the 3rd year, as dictated by approved revised schedule and budget. Dr. PD Schneider of the UC Davis Cancer Center is the co-investigator on the project.

From the 1998 Annual Report ...

There are two substantial contributions of the work. The first is the development of robust pulse sequences and analysis methods to derive accurate T1 estimates with inherently noisy and confounded signal data. The second is the development of the software program (BrView), to allow rapid review, quantitative analysis, and

assessment of the multitude of different breast images and timeseries data that is obtained in each patient study.

Accomplishments relating to Approved Statement of Work

Technical objective 1

Task 1: *Months 1-6: Implementation and testing of magnetization transfer pulses for both arterial tagging and first-pass contrast enhanced sequences.*

Report for 2001

Task completed. No new work was performed for this task.

Report for 2000

Magnetization transfer (MT) was fully tested with the EPI-based spin tagging sequence.

From 1999 Annual Report ...

Magnetization transfer (MT) has been implemented with the EPI-based spin tagging sequence (see Figure 1). The MT radiofrequency (RF) pulse selectively excites the protons of the macromolecules and its hydration layer by a 900 flip angle. Two gradient spoiling pulses (in the x- and y- directions) are applied immediately after the RF pulse to spoil the transverse magnetization. The usual RF excitation pulse for data acquisition is applied immediately after these spoiling pulses. Due to hardware and or compiler problems that are currently being investigated by GE, this pulse sequence has been implemented only on pulse sequence simulation software (EPIC), not yet on the MRI system. The hardware problems are somehow preventing this sequence from running successfully on the MRI system. Testing of MT using the fast SPGR-based sequence revealed that it would not be effective. Because the magnetization transfer RF pulse is long duration (16 ms), the "small TR" (optr) period of the fast SPGR sequence was effectively doubled in length, thus sacrificing short scan time and distorting the signal upon which the perfusion measurement is based.

From 1998 Annual Report ...

Magnetization transfer pulses have not been implemented yet. Mainly, this delay was due to the fact that the MRI system at UC Davis Medical Center is scheduled to be upgraded to the new Horizon LX system soon, and we opted to defer this pulse sequence development until we were using this new LX software platform. There have been multiple delays, but this upgrade is scheduled to occur by January 1999. The existing pulse sequence will be converted from the 5.4 OS platform to the LX2 platform (a substantial change), and the magnetization transfer pulses will be implemented.

Because of concerns regarding the ultimate utility of the magnetization transfer technique, we have decided that implementation and testing of arterial spin-tagging sequence based on echo planar imaging (EPI) data acquisition is a higher priority. EPI based spin-tagging technique can theoretically improve the accuracy of the T_1 estimation, which we have studied and worked with extensively (see below). The major problem with magnetization transfer is that it represents a perturbation on an already small signal. Therefore, whether we will observe a magnetization transfer effect is questionable. Nevertheless, it will be implemented as part of the project.

Task 2: *Months 1-9: Implementation and testing of interleaved high-resolution imaging technique, for both arterial tagging and first-pass contrast enhanced sequences.*

Report for 2001

No new work was performed for this task.

Report for 2000

Conversion of the Fast SPGR Based Arterial Spin Tagging Sequence

The authors completed the conversion and testing of the fast SPGR-based arterial spin tagging pulse sequence, from the Genesis 5.4 platform to the LX 8.2.5 platform.

Development of an EPI-Based Arterial Spin Tagging Sequence

In October 1999, the authors formulated an alternative approach to eliminate the requirement of polarity alternation, which was successfully implemented. The following steps are performed at each interleaf: (1) non-selective RF inversion pulse, (2) 20 EPI acquisitions, each of which is preceded by a 100 RF pulse (Figure 2). These 20 acquisitions are played out with a repetition time (optr in Figure 2) of 100 ms. Each acquisition defines one point on a T1 recovery curve. The total time for each interleaf (TR in Figure 5.10) is 2 seconds. Data for the other interleaves is collected in the same fashion in subsequent TR intervals (see Dissertation). The completed set of images, showing T1 recovery of the magnetization, is acquired in two seconds times the number of interleaves.

From 1999 Annual Report ...

Summary

Since the completion of the upgrade of the UC Davis Imaging Center MRI system, and since it's designation as the Research MRI system for UC Davis, we have thoroughly studied the EPIC LX 8.2.5 programming language for pulse sequence development, and the operation of this new MRI system. The transition to the new research MRI required a complete rewrite of all pulse sequence software that we had developed for this project. In addition, we revised the pulse sequences to utilize the high performance gradients (40 mT/m peak, 150 mT/m/ms rise) of the system. We believe these revised sequences will provide better arterial spin tagged data for perfusion measurement. All of the other sequences in our breast imaging protocol were set up for the new LX 8.2.5 platform as well.

Conversion of the Fast SPGR Based Arterial Spin Tagging Sequence

The authors converted the fast SPGR-based arterial spin tagging pulse sequence from the Genesis 5.4 platform to the LX 8.2.5 platform. The converted sequence was also improved to achieve higher resolution with a shorter overall scan time. The new MR system has higher peak gradient amplitude and slew rate. Fast data acquisition, which requires the higher read-out gradient amplitude (4.0 g/cm) could be specified, and consequently the data acquisition period (optr) was shorten from 16.62 ms to 12.5 ms. Since optr was shortened, a larger matrix in the phase encode direction could be specified. The resolution is now 256 x 256 matrix using a one-half phase field of view acquisition. Previously we used a 256 x 240 matrix with one-half phase field of view acquisition. The total time for the image acquisition (the TR period), including the global inversion RF pulse, has been decreased from 2.7 seconds to 2.22 seconds. The performance of this new sequence has been confirmed using phantoms and one test subject.

Development of an EPI-Based Arterial Spin Tagging Sequence

The EPI-based arterial spin tagging sequence was rewritten and verified on the research MRI system. The data acquisition scheme is based on our recently published high-resolution odd-number interleaf EPI sequence [Buonocore MH, Zhu DC. High spatial

resolution EPI using an odd number of interleaves. Magnetic Resonance in Medicine 41 (6): 1199-1205 (1999)]. This sequence was first developed and verified on the Signa Advantage 1.5 T GE MR system. Unfortunately, under the new LX system, the polarity alternation scheme for each successive interleaf we had implemented caused the system to hang, and substantial time was expended understanding the problem.

From 1998 Annual Report ...

An interleaved arterial spin-tagging technique, that allows high resolution (e.g. 256 x 256 or more) has been implemented and tested. We also implemented a rectangular data acquisition technique, which acquires data sets that have different numbers of points along the frequency and phase encode direction. The 256 x 240 interleaved acquisition provides the best spatial versus temporal resolution tradeoff, and has been used for all of our recent studies.

Task 3*: Months 1-9: Analysis of spin tagging sequence to understand causes of existing baseline offsets, effects of inversion slice transition profiles, and effects of RF flip angle profile on the measurements, with implementation and testing pulse sequence modifications to minimize these imperfections.*

Report for 2001

No new work was performed for this task.

Report for 2000

The EPI arterial spin tagging sequence was not formally evaluated.

From 1999 Annual Report ...

Regarding the spin tagging sequence utilizing fast SPGR, these issues were treated in the 1998 report. The EPI arterial spin tagging sequence has not been evaluated, but the same solutions for the inversion slice transition profiles, and effects of RF flip angle profile, will apply.

From 1998 Annual Report ...

Matching of inversion and excitation slice profiles was greatly improved by using customized RF pulses designed with the Shinnar-Le Roux (SLR) algorithm. The new data processing technique (based on a semi-log linear regression of inversion time (TI) dependent signal) significantly reduced the previously reported problem in measuring the longitudinal relaxation time (T1) caused by baseline offsets, and by the uncertainty in the effective inversion time. The optimal RF flip angle for spin excitation during spatial encoding was found to be 10 degrees, based on experiments over a range of flip angles.

Technical objective 2

Task 4*: Months 3-15: Software for automatic estimation and error analysis of perfusion, tissue water longitudinal relaxation time, and extracellular fluid volume fraction from mathematical models and user-defined ROIs from spin tagging timeseries. Implementation of pharmacokinetic model calculations and error analysis for first-pass contrast enhanced imaging.*

Report for 2001

No new software was developed.

Report for 2000

No new software was developed.

From 1999 Annual Report ...

From October 1998 through April 1999 (during which time there was no MRI system for us to develop on, or do patient studies), image processing software development continued. Improvements in the BreastView program, development of "dispAlls" program for analysis of general MRI images, and implementation of statistical analysis of breast lesions based on Bayesian approach, was completed. Statistical analysis of available breast lesion data continued (See below). The most important new function of BreastView is that for analysis of the first-pass contrast enhanced images. The program creates an image based upon the time derivative of the rate of rise of the signal, so that the contrast enhancement effect can be better visualized (See Figures 4 and 5).

From 1998 Annual Report ...

A software program (BrView) has been written in C, X Window System, and Motif, and implemented on an SGI O2 computer (paid for by grant funds) for analyzing and visualizing the MR images and timeseries. Much effort has been expended on developing the capability to easily review all of the images taken in each study, and cross-reference pixel locations. Much more effort than anticipated was required for development of a robust technique for identifying so-called "suspicious regions" based on the T1 and perfusion measurements. The measurement of T1, upon which the perfusion measurement entirely depends, is based on a semi-log linear regression technique developed by the investigators. The T1, perfusion (f/λ) and standard errors of these quantities are estimated automatically using this robust technique. The so-called feature images display these quantities in color and grayscale. These quantities are used to calculate a "suspicion index" for each pixel, and thereby identify regions of breast tissue suspicious for malignancy.

The implementation of the pharmacokinetic model calculations and error analysis for first-pass contrast enhanced imaging has not been completed. Thus far, the software allows the user to click on the reference image of the dynamic study, to display the time profile of the signal at that pixel. The implementation of the pharmacokinetic model is currently a major focus of the current effort.

Task 5: *Months 3-15: Software for registration (including implementation and testing of motion correction and physiological noise reduction algorithms) and overlay of images from high resolution* T_1 *weighted, spin tagging, and contrast enhanced studies.*

Report for 2001

No new software or software enhancements were developed.

Report for 2000

BreastView

BreastView now performs a simple analysis of first-pass contrast enhanced images. The program creates a contrast enhancement-weighted image based upon the maximum time derivative of the rate of rise of the signal, so that the contrast effect can be better visualized.

The dispAlls program

There were no further enhancements of this program.

From the 1999 Annual Report ...

First described in the 1998 Annual Report, the BreastView program has been continually upgraded and enhanced with the latest algorithms for processing and analysis of breast imaging studies, including those for spin-tagged and dynamic

contrast enhanced images. The specific developments this year of BreastView, and of another program, dispAlls, are described.

BreastView

Between October 1998 and April 1999, the BreastView program was made "clinician-friendly". The graphical user interface now guides the user through the entire visualization and analysis process for a breast imaging study. A "Help" button, linked to extensive set of manual pages, now appears on the first page of the interface. Clicking the Help button brings up an html file with necessary operating instructions. The help files were written for clinicians. The clinician can now begin using the program without first studying the written instructions. If an inappropriate option is selected, the program now provides help to the user to select a more appropriate option or operation. Several new features and functions have been implemented. The most important new function of BreastView is the analysis of the first-pass contrast enhanced images. The program creates a contrast enhancement-weighted image based upon the time derivative of the rate of rise of the signal, so that the contrast effect can be better visualized.

The dispAlls program

This program has been written for quickly viewing and performing ROI analysis on one or a series of images. The program is particularly useful for quickly reviewing the timeseries of signal changes in an ROI from the dynamic contrast enhanced studies. The program displays one image, or a sequence of images, with or without an image header. It performs ROI analysis and plots the calculated values.

From 1998 Annual Report ...

Using the BrView software program, image pixels containing high values of perfusion (f/λ), and moderate to high values of T_1, and low standard errors, are identified as suspicious, and assigned a "suspicion index" based on finding similar abnormal values at spatially adjacent pixels. Suspicious pixels can be overlaid on the high-resolution T_1 and T_2 clinical images by color mapping, and simultaneously presented with the first-pass contrast enhanced timeseries at these pixels. This provides the user with a comprehensive anatomical and functional view of the suspicious regions, and facilitates making a decision regarding the malignant nature of the lesion. Finally, a motion artifact estimation and correction algorithm has been developed and implemented in a separate software program.

Technical objective 3

Task 6: *Months 9-24: 60 patients with malignant and benign breast lesions will be imaged using* T_1 *weighted, first-pass contrast enhanced, and arterial spin tagging MRI pulse sequences.*

Report for 2001

No additional subjects have been studied. The mechanism to recruit subjects was ineffective. We have asked for another one-year no-cost extension to accomplish this task. The no-cost extension approval documentation is included in the Appendix. This documentation includes a full explanation, written by the principal investigator, stating why recruitment was not effective this year and why recruitment is more likely to occur this year.

Report for 2000

No additional subjects have been done.

From the 1999 Annual Report ...

Unfortunately, no additional subjects have been done. This is due to the loss of Rebecca Zulim, MD, as the co-investigator, and the transition to a dedicated research

MRI system that operated at LX 8.2.5, as described above. Through Sept 1998, eighteen subjects, including 11 patients referred by their physicians and seven self-referred volunteers, had participated in the breast studies. Three patients and two volunteers were eliminated from the analysis because the studies were not done according to protocol, due to excess motion, or the abnormal mass being too close to the chest wall to be measured reliably, or no patient biopsy to confirm the MR study result. There are total of 13 useful cases left for analysis. For all these cases, the suspicious pixels were identified based on the following criteria: T1n: > 0.5 sec f/???> 0.1 sec-1, STD of f/?: < 0.1 sec-1, and the suspicion level threshold was set at 20.2%. Analysis has been done using the program BreastView. Table 8.5 shows the result of these 13 cases.

From 1998 Annual Report …

We have thus far recruited two subject studies for both first-pass contrast enhanced and arterial spin tagging MRI pulse sequences. Now that the software development is substantially completed, we are trying to improve the rate at which patients are recruited into the study. It is likely that the patient studies will extend into the third year of the proposal. We are currently discussing with physicians at a local Kaiser Hospital for recruitment of additional patients. Appropriate documentation will be submitted for approvals upon reaching a firm agreement.

Task 7 (listed as Task 6 in the original grant application): *Months 12-36: Automated pharmacokinetic analysis, blinded image reading, and statistical comparison of arterial spin tagging, contrast enhanced MRI, and biopsy results.*

Report for 2001

No new software was developed.

Report for 2000

No new software was developed.

From the 1999 Annual Report …

We developed an analysis program for the detection of the features of the dynamic contrast enhanced study, and have developed a statistical approach to the determination of the malignant status of the lesion.

Bayesian Statistical Analysis

The identification of a suspicious pixel based upon the index threshold, that was developed last year, is a simple approach to cancer detection. When a large number of studies become available, a Bayesian decision technique [53] will be applied. This technique will be used to provide ROC (receiver operating characteristic) curves that are commonly used for evaluation of diagnostic algorithms. To summarize the Bayesian technique, let vector space x = (T1, f/λ, STD of f/λ, etc.) for a ROI (region of interest) in a breast.

From the 1998 Annual Report …

Automated pharmacokinetic analysis, blinded image reading, and statistical comparisons, have not been started.

Key Research Accomplishments

Report for 2001

There were no new key research accomplishments.

Report for 2000

A. EPI-based arterial spin tagging sequence, with MT pulse option, for Signa Horizon LX CV/i system.

From the 1999 Annual Report ...

A. Pulse sequences that are compatible with a Signa Horizon LX EchoSpeed CV/i system, running LX 8.2.5 system software:

1. Fast SPGR-based arterial spin tagging sequence
2. Odd-number interleaved EPI sequence
3. Interleaved EPI-based arterial spin tagging sequence

B. Imaging processing software

1. BreastView
2. DispAlls
3. Bayesian analysis of arterial spin tagged image data

From the 1998 Annual Report ...

A. Fast SPGR-based arterial spin tagging sequence for Signa Advantage MRI system, running 5.7 system software:

B. Imaging processing software (BrView)

Reportable Outcomes

Report for 2001

There were no new reportable outcomes.

Report for 2000

A. Buonocore MH, Zhu DC. Magnetic resonance arterial spin tagging for non-invasive pharmacokinetic analysis of breast cancer. Poster Presentation and Abstract. Proceedings of the Era of Hope, Dept. of Defense Breast Cancer Research Program Meeting, June 8-11, 2000, Hilton Atlanta and Towers, Atlanta, GA, Vol. 1, page 177.

B. Buonocore MH, Zhu DC, Zulim RA. Magnetic resonance arterial spin tagging for non-invasive pharmacokinetic analysis of breast cancer. Poster Presentation and Abstract. Proceedings of the UC Davis Cancer Center Symposium, Oct 6-7, 2000. UC Davis Cancer Center, Sacramento, CA.

C. David Zhu. PhD Dissertation. Magnetic resonance pulse sequences and analytical techniques for breast cancer detection and cardiovascular flow. UC Davis, Biomedical Engineering. Dec 1999.

D. David Zhu. PhD in Biomedical Engineering, Dec 1999.

E. David Zhu, PhD. Employment as GE Applications Engineer, beginning Jan 2000.

From the 1999 Annual Report ...

F. Buonocore MH, Zhu DC. High spatial resolution EPI using an odd number of interleaves. Magnetic Resonance in Medicine 41 (6): 1199-1205 (1999).

G. Buonocore MH, Zhu DC, Zulim RA. Analysis software for breast imaging studies. Proceedings of the International Society for Magnetic Resonance in Medicine, 7th Annual Meeting and Exhibition, 3: 2172 (1999).

H. Pulse sequences for Version 8.2.5 (MH Buonocore and D Zhu):

Arterial spin tagging sequence with Fast SPGR Acquisition

Odd-number interleaf EPI

Arterial spin tagging sequence with Odd-number interleaf EPI acquisition

Arterial Spin Tagging sequence with Even-number hybrid EPI acquisition

I. Breast Imaging Protocols (MH Buonocore and D Zhu)

Anatomical, spin tagged, and dynamic c-e breast imaging protocol

J. SGI Graphics Software for Breast image analysis (MH Buonocore and D Zhu):

BreastView (display program for breast imaging protocol)

DispAll (display program for general MRI images)

From the 1998 Annual Report ...

A. Buonocore MH, Zhu DC. Odd-number hybrid EPI. Proceeding of the International Society for Magnetic Resonance in Medicine, 6th Annual Meeting and Exhibition, on CD-ROM, p. 1967 (1998).

B. Buonocore MH, Zhu D, Pellot-Barakat C. Measurement of breast tissue perfusion using arterial spin tagging, Proceedings of the International Society for Magnetic Resonance in Medicine 5th Annual Meeting and Exhibition, 1: 311 (1997).

C. Buonocore MH, Zhu DC, Pellot-Barakat C, Zulim RA. Noninvasive measurement of blood flow through breast tumors. Book of Abstracts, California Breast Cancer Research Symposium. Sacramento Convention Center, Sacramento CA, Sept. 16, 1997.

D. Buonocore MH, Zhu DL, Pellot-Barakat C., Zulim RA. Non-invasive measurement of breast tissue perfusion using arterial spin tagging. Radiology, November 1997, 205 (P): 162.

E. Sequence and Protocols for arterial spin tagging for Version 5.7 Signa Advantage MRI

F. Software for display and analysis of breast images, written in C, X and Motif.

Conclusions

Report for 2001

Technical accomplishments over the past four years have been documented in a PhD Dissertation, a CD ROM of research software, and poster presentations. These will be used to accomplish the third Specific Aim of the project, to non-invasively measure perfusion parameters in breast masses prior to biopsy. These measurements may distinguish malignant from benign breast lesions. From Sept. 30, 2000 through Sept. 29, 2001 the project was inactive. We requested and received approval for a no-cost extension through Sept 29, 2002 for patient recruitment.

Report for 2000

Technical accomplishments over the past three years have been documented in a PhD Dissertation, a CD ROM of research software, and poster presentations. These will be used to accomplish the third Specific Aim of the project, to non-invasively measure perfusion parameters in breast masses prior to biopsy. These measurements may distinguish malignant from benign breast lesions.

From the 1999 Annual Report ...

We have successfully converted and enhanced the arterial spin tagging pulse sequences to work on a new research MRI system, and have made several enhancements. Understanding of the 8.2.5 pulse sequence language on the new system represents a major advance of the project. These pulse sequences will be used in all future work, and hopefully there will not be a substantial MRI system upgrade such as we experienced for a few years at least. Image display and statistical analysis software has been written for the spin tagging and contrast enhanced studies, and to allow analysis to be done by a busy clinician without computer expertise.

From the 1998 Annual Report ...

In this year of the project, we have developed the necessary pulse sequences for anatomical and functional imaging of breast tissue, and the necessary software for the analysis, display and interpretation of this data. These developments will allow us to evaluate complete breast imaging studies that are composed of anatomical scans, dynamic first pass contrast enhanced scans, and arterial spin tagging scans. The integrated nature of the software allows easy and consistent interpretation of both spatial dependencies as well as temporal dependencies of signal changes indicative of disease. The in-vitro and in-vivo studies done thus far indicate that first and foremost, arterial spin tagging is a sensitive and reliable method for measuring T1 and parameters related to tissue perfusion. Second, they indicate that arterial spin tagging is a viable alternative to dynamic first-pass contrast-enhanced imaging. The fact that arterial spin tagging can be easily added to any standard breast imaging protocol, without requiring special nursing or MR technologist expertise, means that it is especially attractive for routine clinical use. It could be used to supplement contrast-enhanced studies in the initial study of the patient, and used exclusively in follow-up studies. Since 10/1/98, six subjects have been studied without the dynamic first-pass contrast-enhanced scan, and two have been studied with this scan. Comparison of contrast-enhanced images versus arterial spin-tagged images has not yet been made. In particular, no statistical comparison of the dynamic study results (considered to be the gold standard for non-invasive assessment of malignant disease) with the arterial spin tagging results has been performed. However, there is considerable spatial overlap of suspicious regions obtained by these methods noted on visual inspection. Collecting data on human subjects, and statistical confirmation of this agreement, will be major focuses of next year's work.

References

Report for 2001

No additional references.

Report for 2000

1. Buonocore MH, Zhu DC. Magnetic resonance arterial spin tagging for non-invasive pharmacokinetic analysis of breast cancer. Proceedings of the Era of Hope, Dept. of Defense Breast Cancer Research Program Meeting, Vol. 1, page 177 (2000).

2. Buonocore MH, Zhu DC, Zulim RA. Magnetic resonance arterial spin tagging for non-invasive pharmacokinetic analysis of breast cancer. Proceedings of the 6th Annual UC Davis Cancer Center Symposium, Oct 6-7, 2000.

From the 1999 Annual Report ...

3. Buonocore MH, Zhu DC. High spatial resolution EPI using an odd number of interleaves. Magnetic Resonance in Medicine 41 (6): 1199-1205 (1999).

4. Buonocore MH, Zhu DC, Zulim RA. Analysis software for breast imaging studies. Proceedings of the International Society for Magnetic Resonance in Medicine, 7th Annual Meeting and Exhibition, 3: 2172 (1999).

From the 1998 Annual Report ...

5. Buonocore MH, Zhu DC. Odd-number hybrid EPI. Proceeding of the International Society for Magnetic Resonance in Medicine, 6th Annual Meeting and Exhibition, on CD-ROM, p. 1967 (1998).

6. Buonocore MH, Zhu D, Pellot-Barakat C. Measurement of breast tissue perfusion using arterial spin tagging, Proceedings of the International Society for Magnetic Resonance in Medicine 5th Annual Meeting and Exhibition, 1: 311 (1997).

7. Buonocore MH, Zhu DL, Pellot-Barakat C., Zulim RA. Non-invasive measurement of breast tissue perfusion using arterial spin tagging. Radiology, November 1997, 205 (P): 162.

Appendices

One-year no-cost extension approval (Administrative Agreement effective Sept 30, 2001 through Sept 29, 2002), including justification of request.

ASSISTANCE AGREEMENT

AWARD TYPE: ☑ GRANT (31 USC 6304) ☐ COOPERATIVE AGREEMENT (31 USC 6305) ☐ OTHER TRANSACTION (10 USC 2371)

AWARD NO: DAMD17-97-1-7030 Modification P00005	EFFECTIVE DATE See Grants Officer Signature Date Below	AWARD AMOUNT $262,236.00	Page 1 of 1 Rita Johnson 301-619-2359 301-619-4084

PROJECT TITLE: Magnetic Resonance Arterial Spin Tagging for Non-Invasive Pharmacokinetic Analysis of Breast Cancer (BC961359) **CFDA 12.420**

PERFORMANCE PERIOD: 30 Sep 1997 - 29 Oct 2002
(Research shall end 29 Sep 2002)

PRINCIPAL INVESTIGATOR:
Michael H. Buonocore, M.D., Ph.D.

AWARDED AND ADMINISTERED BY:
U.S. Army Medical Research Acquisition Activity
ATTN: MCMR-AAA-A
820 Chandler St.
Fort Detrick Maryland 21702-5014

PAYMENTS WILL BE MADE BY: **EFT:T**
Army Vendor Pay
DFAS-SA/FPA
500 McCullough Avenue
San Antonitio, TX 78215-2100
(SEE PARAGRAPH TITLED "PAYMENTS" FOR INSTRUCTIONS)

DUNS No: 003985512 **TIN No:**

AWARDED TO:
The Regents of the University of California
University of California
Office of Vice Chancellor Research
410 Mrak Hall, One Shields Avenue
Davis, CA 95616-8671

REMIT PAYMENT TO:
The University of California, Davis
Cashier's Office
173 Mrak Hall, One Shields Aveu
Davis, CA 95616

ACCOUNTING AND APPROPRIATION DATA: No Change

SCOPE OF WORK:

The subject Assistant Agreement is hereby extended for 12 months without additional funds. This action is in accordance with the recipient's email, dated 15 Oct 2001, which is incorporated herein by reference.

PERFORMANCE PERIOD:

FROM: 30 Sep 1997 - 29 Oct 2001
(Research ends 29 Sep 2001)
TO: 30 Sep 1997 - 29 Oct 2002
(Research ends 29 Sep 2002)

ALL OTHER TERMS AND CONDITIONS REMAIN UNCHANGED.

TOTAL AMOUNT ALLOTTED FOR AWARD: $262,236.00

Reviewed & Processed
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Date 11/16/01
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☒ Dept: Radiology
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☐ Engr. Dean
☒ Med. Dean
☐ VM Dean
☐ Other

RECIPIENT		GRANTS OFFICER	
ACCEPTED BY: NO SIGNATURE REQUIRED. REFERENCE RECIPIENT'S EMAIL DATED 15 Oct 2001 FOR SIGNATURE. SIGNATURE		**UNITED STATES OF AMERICA** Patricia A. Evans SIGNATURE	
NAME AND TITLE	**DATE**	**NAME AND TITLE** PATRICIA A EVANS GRANTS OFFICER	**DATE** 25Oct01

Michael H. Buonocore

From: Johnson, Marquerita E Ms USAMRAA [Marquerita.Johnson@DET.AMEDD.ARMY.MIL]
Sent: Tuesday, October 16, 2001 4:39 AM
To: 'Fay Yee'; Johnson, Marquerita E Ms USAMRAA
Cc: Buonocore, Michael; Jennifer O'Rell
Subject: RE: No-cost extension on DAMD-17-97-1-7030

Thank you

-----Original Message-----
From: Fay Yee [mailto:FFYee@Research.UCDavis.Edu]
Sent: Monday, October 15, 2001 5:23 PM
To: 'Marquerita.Johnson@DET.AMEDD.ARMY.MIL'
Cc: Buonocore, Michael; Jennifer O'Rell
Subject: FW: No-cost extension on DAMD-17-97-1-7030
Importance: High

Dear Ms. Johnson,

Please consider this email as institutional concurrence of Dr. Buonocore's request below. Please feel free to contact me with any additional concerns.

-Fay Yee
Contracts and Grants Analyst
Office of the Vice Chancellor for Research
Sponsored Programs, 118 Everson Hall
One Shields Avenue
University of California
Davis, California 95616-8671
* Phone (530) 752-6839 Fax (530) 752-5432
* *
Please visit the OVCR website at http://ovcr.ucdavis.edu
* *
Notice: The Sponsored Programs Office of the OVCR has moved. Please note new address.
* *

-----Original Message-----
From: Michael H. Buonocore [mailto:mhbuonocore@ucdavis.edu]
Sent: Monday, October 15, 2001 10:46 AM
To: Rita Johnson
Subject: No-cost extension on DAMD-17-97-1-7030

Dear Ms. Johnson,

I am writing to request a one year no-cost extension of grant DAMD-17-97-1-7030. During the past year, the project has been inactive, and no funds have been expended. In the paragraphs below I explain the history of project progress, and provide reasons why I believe that the project objectives can be completed over the next year.

Last year at this time (Sept 29, 2000) I received a one year no-cost extension of the grant. At that time, the grant objectives had not been completed because my co-Investigator, Rebecca Zulim, MD (oncology surgeon) who was responsible for recruitment and evaluation of the patients, left the Medical Center. At that time (one year ago), I anticipated that the studies could be completed with the help of a new faculty member in Radiology, Dr. Edward Lee. Dr. Lee and

I developed a plan for recruitment that remains a valid approach today.

The project has remained inactive over the past year, due to other difficulties. In late 2000, I anticipated finding another graduate student to continue the efforts of David Zhu, whose PhD dissertation on arterial spin tagging was submitted in last year's annual report. I was hopeful that Gina Belleau, a master's student who had worked with me on imaging of breast viscoelasticity, would accept this work. However, Gina chose to work on another project with me. She is currently employed as a technical writer for two MRI books.

I quickly found that the time that would be required to analyze the breast arterial spin tagging data was much more than I could afford to give. The work of acquiring and analyzing the data required a full time graduate student. My lack of time for analyzing the data was further reduced by my acceptance in July 2000 of the Technical Directorship of MRI for the Radiology Department. Furthermore, in April 2001, I accepted the Technical Directorship of the new Imaging Research Center of the UC Davis Health System. These responsibilities have taken away from time I might have spent on the data analysis.

The Imaging Research Center, a new facility established in July 2001, provides an ideal setting for the breast imaging study. It currently houses a GE 1.5T CV/I system. Trained technical staff and credentialed MRI operators provide all the services needed to carry out the scanning sessions. Prior to July 2001, this system was managed by the Radiology Dept, and was the system on which the breast imaging studies were to be performed. Technical staff and credentialed MRI operators for support of research were not provided under Radiology management, making projects difficult to orchestrate. Therefore, the environment for performing the breast imaging study has greatly improved.

An outstanding biomedical engineering graduate student, Mahmoud Abdulhusain, has this summer begun his PhD dissertation work on arterial spin tagging under my supervision. Mahmoud has taken all four of my graduate MRI courses and is well prepared for research. He will devote the first year of his dissertation work to this arterial spin tagging project.

If you have further questions or need more documentation, please do not hesitate to write or call. Thank you for your consideration. I look forward to hearing from you.

Sincerely,

Mike Buonocore

Cc: Fay Yee, UC Davis Contracts and Grants Office

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Technical Director, UC Davis Imaging Research Center
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